Bio-Design and Manufacturing (2018) 1:203–210
https://doi.org/10.1007/s42242-018-0021-2

SHORT PAPER

Application of 3D printing technology in bone tissue engineering

Kang Ji[1] · Yanen Wang[1] · Qinghua Wei[1] · Kun Zhang[1] · Anguo Jiang[1] · Yiwen Rao[1] · Xianxuan Cai[1]

Received: 17 July 2018 / Accepted: 8 August 2018 / Published online: 22 August 2018

Introduction

Bone defect caused by specific diseases or medications is very common. Autologous bone, allogeneic bone or xenogeneic bone transplantation is commonly used in clinical practice. However, autologous bone sources are limited. Xenogeneic bone cannot participate in metabolism. Because of the development of bone tissue engineering, the transplantation of new scaffold materials and autologous cells has opened up new treatment options for bone defects. The bone tissue engineering principle is applied to construct a degradable porous bone scaffold, which is implanted into the human body after loading bone cells, growth factors, etc. [1]. These scaffolds can be decomposed and absorbed by bone cells to form new bone. As a template for cell planting and tissue regeneration, the preparation of bone scaffolds has become an important part of bone tissue engineering, which is also a bottleneck restricting the clinical application of bone tissue engineering. Ideal scaffold needs to have good biocompatibility, biodegradability and suitable mechanical strength [2]. It is difficult for traditional bone grafting techniques to prepare individualized scaffold according to the structural characteristics of specific lesions, and the internal pore structure is also difficult to effectively control. 3D printing technology meets these needs very well, which can accurately produce personalized tissue engineering bone scaffolds based on bone defect and CT imaging data, and match the scaffold with the defect areas perfectly, imitate the normal nature tissue microstructure of human. With the continuous updating of 3D printers, seed cells and scaffold materials can be printed simultaneously, and the differentiation of osteoblasts is accompanied by the biodegradation of biomaterial. Some scholars have used the 3D printing technology to prepare human maxillary and mandibular scaffold models based on CT scan data and induced intravascular regeneration [3].

✉ Yanen Wang
wangyanen@nwpu.edu.cn

[1] Industry Engineering Department, School of Mechanical Engineering, Northwestern Polytechnical University, Xi'an 710072, People's Republic of China

Principles of bone tissue engineering

In order to fundamentally understand the changes in pathological tissue structure and function, and to develop biological substitutes for repairing damaged tissues, tissue engineering has emerged [4]. The repair of bone defects caused by lesions or trauma is an important part of tissue engineering. Due to the different sites of bone defects, the constructed artificial bones have different structures, sizes, and biomechanical strengths. The traditional method of constructing is to inoculate osteogenic functional cells on a three-dimensional scaffold material in vitro and implant them into the human body after a period of culture to repair the bone defect tissue. Another way is to repair bone defect in vivo, which is using active growth factors or osteogenic functional materials to induce the osteogenesis of autologous tissue (periosteal or mesenchyme cells). The whole repair or reconstruct process is demonstrated in Fig. 1 [5, 6].

Function of bone scaffold

In general, bone tissue engineering consists of three basic elements, which is cells, growth factors and bone scaffolds [7, 8]. As a framework for bone tissue regeneration, scaffold materials directly affect the biological properties of seed cells, such as its survival, migration, proliferation and metabolism. This scaffold plays the following roles in vivo:

(1) As a scaffold for inoculated of cells in vitro, directing tissue grow into specific morphology.
(2) Provide support for the defect site and hinder the growth of other surrounding tissues.
(3) As a carrier of the signal molecules, transport those single molecules to the defect site and act as a sustained release body to slowly functioning.
(4) As a place for the differentiation and metabolism of bone tissues, transporting nutrients and metabolic waste for cell growth.

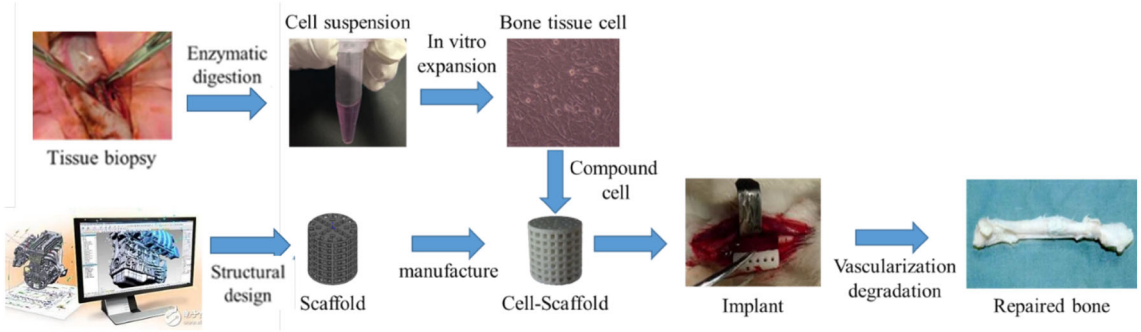

Fig. 1 Bone tissue regeneration process

(5) Binding to specific cells, screening and selective adhesion to different types of cells.

Performance of materials for bone engineering

The ideal bone scaffold should be able to repair the bone defect and restore the bone tissue function to the greatest extent, and the system inside the body is extremely complicated, so the stent should meet the following requirements:

Biocompatibility

Biocompatibility refers to the performance of non-biological materials implanted in the body to cause autologous biological tissue reactions, which is related to the safety of the stent during clinical use [1]. Good biocompatibility requires that the scaffold material has good surface physicochemical properties to ensure normal adhesion and growth of the cells; the scaffold does not cause inflammatory reaction, any immunogenicity and cytotoxicity, and the degradation rate should be related to tissue growth. The speed is consistent, achieving a smooth transition from the stent to the ontogenesis [9, 10].

In addition, during the degradation of the scaffold, the tissue cells are provided with a constantly changing interface for adhesion and growth, which contributes to the firm adhesion of the cells to the material.

Osteoinductivity and osteoconductivity

In tissue engineering, the scaffold should not only serve as a carrier for cell proliferation, but also combine certain substances to induce the natural growth of bone tissue. There are two aspects: Firstly, the stent should have osteoconductivity. After being implanted into the human body, it can realize osteoblast transplantation, proliferating host bone tissue cells into the internal pores of the scaffold, and gradually dissolve the scaffold to form a new extracellular matrix. Secondly, the scaffold usually combines bone growth factors, which will be slowly released after implantation, and induces mesenchyme cells to differentiate into bone at non-skeletal tissue sites [11].

The three-dimensional (3D) microenvironment and porous matrix of the bone scaffold with good osteoconductivity enable the immigration of the bone cell along the surface or internal pores of the fabricated construct. The newly formed osteoblasts in bone scaffolds with good osteogenesis have the potential for further mineralization and formation of new external bone construct. Therefore, many scientists and technician have improved the osteoinductivity of bone scaffolds, by changing their physical and chemical properties or by incorporating biological constitute into the scaffolds [12]. Moreover, the porosity and pore topology structure of bone scaffolds can be modified, to enhance the osteoconductivity [13, 14].

Mechanical performance

The ideal bone scaffold needs to have mechanical properties that match the bone of the defect site, and the scaffold can always perform a perfect function from the beginning of implantation to the completion of the body repair [15–18]. Excessive hardness of the bone scaffold produces stress shielding. The load cannot transfer from the implant to the adjacent bone tissue, resulting in insufficient mechanical stimulation of the filled autologous bone and primitive cancellous bone. As the stent structure degrades, the implant gradually loosens, eventually leading to bone repair and reconstruction failure [19, 20]. Conversely, if the stiffness is too low, the load carrying capacity will be reduced and the bone will be more easily broken. Therefore, the scaffold cannot meet the mechanical strength requirements [21].

The scaffold material generally has a high porosity to facilitate the invasion and transport of host cells, and the corresponding mechanical strength is inevitably decreased. At the same time, the differences between different individuals are relatively large. Young individuals usually start weight bearing after 6 weeks of fracture. After about 1 year, the

mechanical properties of the fracture site can be restored to the pre-injury level, while the recovery process of elderly individuals is relatively slow.

Among the existing scaffold materials, the organic material has a high elastic modulus, but the mechanical strength is low; while the bioceramic is brittle, the body is easily crushed. The combination of the two can obtain better mechanical properties, and the addition of chemical surfactant can increase the bonding energy between the composite interfaces, improve the dispersion of bioceramic particles in the organic phase and effectively improve the biomaterial of the scaffold material [22, 23].

Microstructural features

In addition to macroscopically connected pores (pore size > 50 μm) for excellent vessel growth and material transport [6], suitable microscopic pores (pore size < 50 μm) are also key to optimal osteogenesis [24]. Pore structure parameters, including pore size, porosity, connectivity between pores, degree of distortion of connected pores, and surface area, affect osteogenesis. The high-dimensional three-dimensional pore structure and high porosity significantly increase the specific surface area of the stent, which can ensure cell attachment and nutrient transport, and facilitate the smooth discharge of cellular metabolic waste and scaffold degradation products. The study found scaffold can achieve cell attachment, angiogenesis, nutrient transport, and metabolic waste discharge should have porosity more than 90% [25, 26].

Also, the extent of bone ingrowth depends on the pore size [27, 28]. The ideal pore diameter of scaffold materials should be similar to the size of the normal bone unit. (The average size of the human bone unit is about 223 μm.) Generally, a scaffold pore diameter ranging between 200 and 400 μm is considered adequate [29]. At the same time, some scholars have pointed out that it is not the size of the pores that restricts the invasion of bone tissue into the pores, but the degree of connectivity between the pores [30].

Bionic design of scaffolds for bone reconstruction

Biologically, bone tissue is a tough connective tissue composed primarily of cells, fibers, and stroma. The fiber is bone rubber fiber. There is a large amount of calcium deposits in the matrix. The cells mainly include osteoblasts, bone cells and osteoclasts. As shown in Fig. 2, the bone structure is divided into dense bone and cancellous bone. The dense bone consists of bone units composed of bone plate layer arranged by Harvard tube and its surrounding concentric layer. The cancellous bone is three-dimensional porous trabecular framework.

From the perspective of materialogy, biological bones are mainly composed of mineral salts and biological proteins. Inorganic mineral salts in bone tissue account for 60–70% of dry bone weight, most of which are hydroxyapatite [31]. Organic proteins account for about 30–40% of the dry bone weight, of which about 95% are type I collagen, which is ordered by the triple-stranded polypeptide chain, arranged in an order around the hydroxyapatite. In summary, the biological bone is formed by depositing calcium phosphate minerals on an ordered array of collagen substrates.

In tissue engineering, it is generally accepted that bionic design determines whether the biological structures prepared in vitro can survive in vivo, as well as whether the surviving bone tissue has proper biological functions. The bionic design of bone scaffolds includes the bionic structure design and bionic performance design. The existing bionic designed scaffold has the dense bone and cancellous bone structure of the human bone. Bionic designed sheep spine is shown in Fig. 3c, the problem of low strength of single porous structure is overcome, and the nutrient supply and shape matching of the bone scaffold can be ensured. At the same time, the mechanical properties of the compact bone are very high, and the mechanical properties of the cancellous bone vary greatly from person to person, and the individual bones have different lengths, complex surfaces and different joint angles. Therefore, it is still difficult to fabricate bone scaffold by taking both the spatial structure of natural bone and mechanical properties into account [21, 24, 32].

Formation methods of bone scaffolds

Numerous conventional techniques including solvent casting with particulate leaching, fiber bonding, membrane lamination, freeze drying, and gas foaming were developed to fabricate porous scaffolds [33, 34]. Although these techniques applicable to the preparation of porous scaffolds, but incapable of precisely controlling pore size, geometry and pore interconnectivity, the appearance is also unable to fully fit the defected bone tissues and therefore cannot be adapted to fabricate personalized scaffolds [35].

In addition, the size of the scaffold is often limited due to difficulties in removing pores and some of these conventional techniques use toxic organic solvents that may partially remain in the scaffold post-processing.

Rapid prototyping is well suited to the needs of tissue engineering for its advantages of high precision, high construction speed and capable of formation of complex structures to meet personalized medical needs and rejection reactions [36]. Additionally, additive manufacturing enables the incorporation of drugs/proteins as well as cells during scaffold

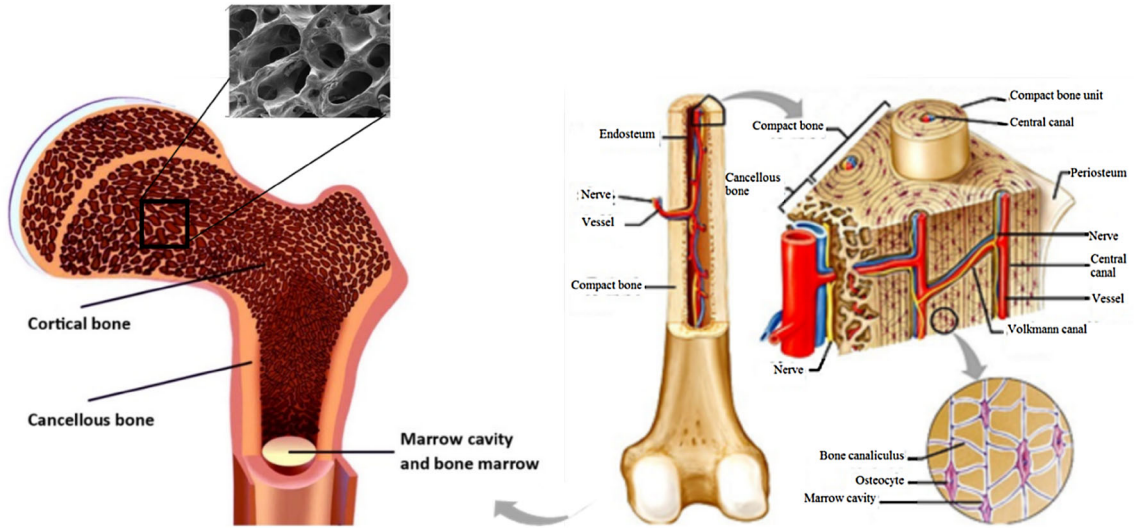

Fig. 2 Anatomical structure of biological bone

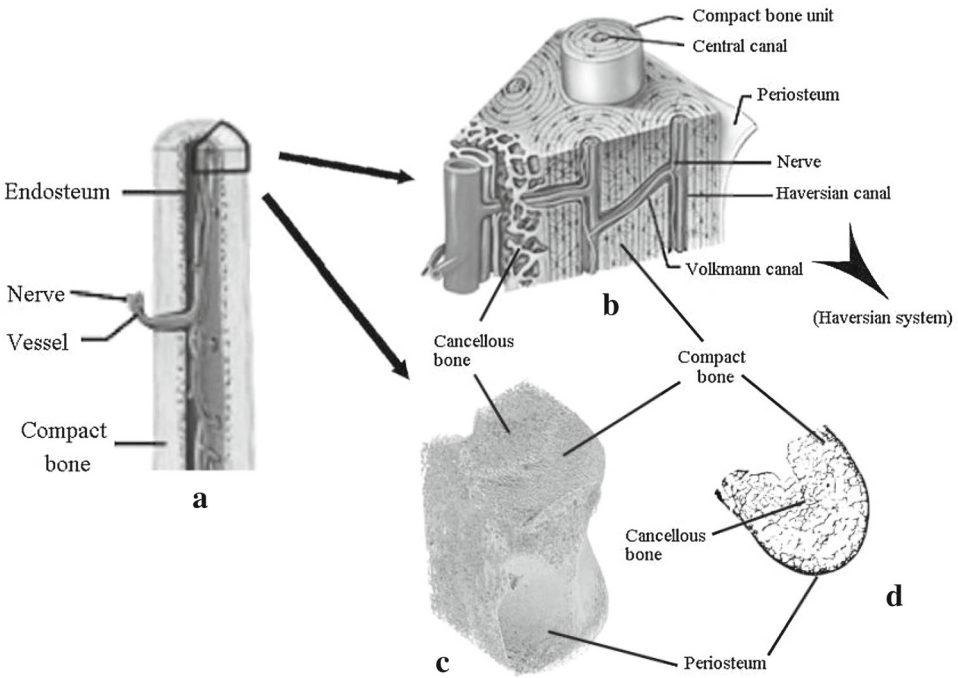

Fig. 3 Bionic designed bone scaffolds before 3D fabrication [32]

manufacturing to produce very complex architecture similar to bone [37–39]. Therefore, additive manufacturing methodology is widely used for the formation of biological bone scaffolds.

In the process of personalized preparation of the porous structure and shape of the tissue engineering scaffold, the structure and shape of the damaged part are usually reconstructed in combination with medical CT scanning technology, and the rapid and accurate preparation of the scaffold is realized by means of rapid prototyping technology. The commonly used molding methods for preparing bone scaffolds can be classified into three types: laser-based molding systems such as photo-curable molding (SLA), selective laser sintering (SLS); nozzle-based extrusion molding systems such as fused deposition molding (FDM), Pneumatically assisted extrusion deposition (PDM); injection molding systems based on inkjet printing, such as three-dimensional forming (3DP), pneumatic micro-valve injection molding (PAM).

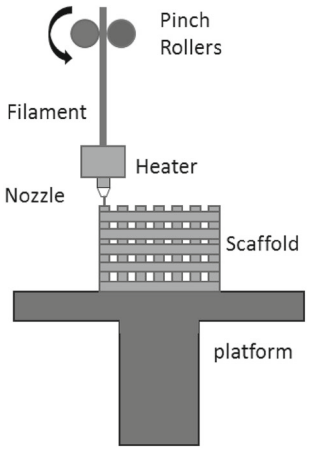

Fig. 4 Schematic diagram for FDM molding system

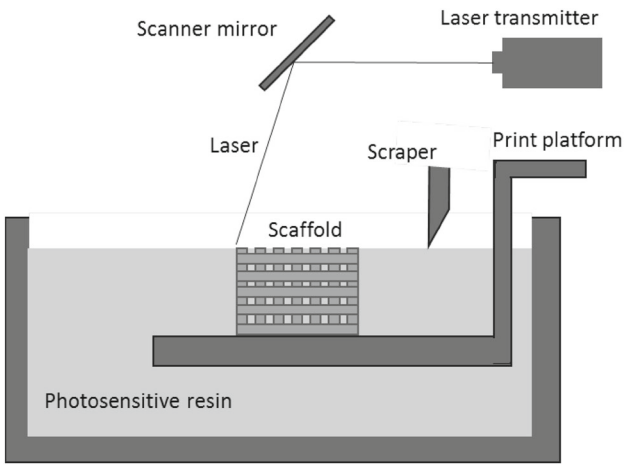

Fig. 5 Schematic diagram for SLA molding system fabricating scaffolds

Fused deposition molding

The smelting deposition molding process is shown in Fig. 4. The filamentous thermoplastic material such as ABS, metal fuse or wax is used as raw material, and the raw material is fed into the nozzle by a pinch roller or a screw feeding mechanism and then heated under computer control. The nozzles are sequentially pressed to the printing platform according to the path of the model layered processing and then stacked layer by layer to complete the model construction. The structure of the model is determined by factors such as nozzle diameter, deposition rate, path spacing of the same layer, layer thickness and deposition angle.

FDM technology molding process is flexible and easy to control, and the application is more common. In addition to the early use of collagen, ceramics, PLGA and printing consumables, researchers have continued to experiment with composite materials and nanomaterials in recent years to obtain superior printing performance. Li et al. [40] demonstrated that PCL-TCP scaffolds can better promote bone growth and distribution by comparing the effects of titanium alloy and FDM molded PCL-TCP scaffolds as spine cages. Zein et al. [41] used FDM technology to prepare degradable porous scaffolds using filamentous polycaprolactone (PCL). Dong et al. [42] fabricated three-dimensional (3D) porous β-tricalcium phosphate (β-TCP)/calcium silicate (CS) composite scaffolds with different ratios by this kind of 3D printing technique. The scaffolds were composed of oriented filaments with an internal pore size of 160–200 μm and a porosity of 48–77%, and the strength of the bracket is highly related to the grid structure.

At the same time, there are some defects in FDM molding, such as the need for heating in the molding process, which can easily lead to degradation of polymer materials, inactivation of biological macromolecules, and is not conducive to compound biological factors. Long molding time, difficult to form the microporous structure of bionic bones and the smooth surface of the model, is not conducive to cell adhesion.

Stereolithography

Stereolithography is a kind of photopolymerization molding. Using the principle of photopolymerization of photosensitive resin, a specific wavelength and intensity of the laser are used to track the single-layer motion trajectory of the model so that the photosensitive material is solidified and formed, and then the movement of the lift table is completed to perform layer-by-layer scanning into a complete model (Fig. 5).

The advantage of SLA is high resolution. The appearance of micro-stereolithography (MSLA) allows it to achieve an accuracy of 20 μm, allowing for the formation of more precise parts. Lee et al. completed polypropylene fumarate (PPF) with polylactic acid microspheres (PLGA) loaded with bone morphogenetic protein (BMP-2) and prepared highly connected porous scaffolds using MSLA technology [43]. Growth factors are gradually released during in vitro culture, and osteoblasts differentiate well, which provides an idea for the preparation of bone scaffolds. The main drawback of SLA is the lack of available biocompatible materials, and researchers are also experimenting with new composites. Ronca et al. used polylactide and nano-hydroxyapatite as substrates to obtain higher strength and better biocompatibility through SLA synthesis of composite scaffolds [44].

Selective laser sintering

The difference between selective laser sintering and SLA is that the substrate is in powder form. In the molding process, the powder material is first laid on a printing platform, and the cross-sectional shape of the model is scanned with a laser

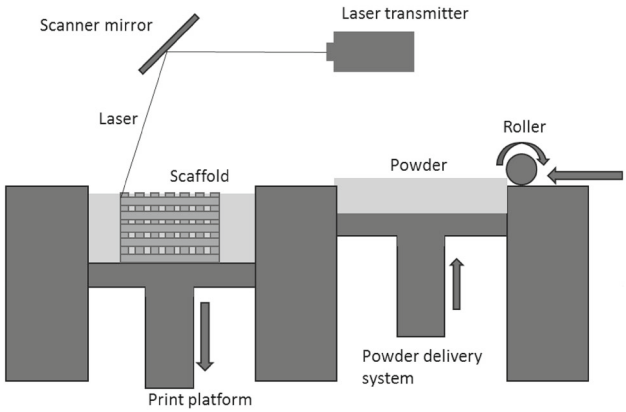

Fig. 6 Schematic diagram for SLS molding system for fabricate scaffold models

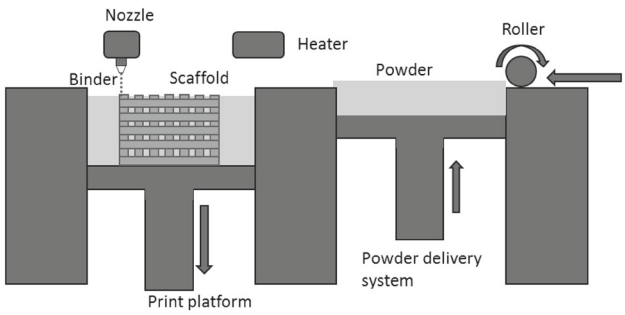

Fig. 7 Schematic diagram for 3DP molding system

to perform selective sintering. Then, the lifting platform is adjusted and a new layer of powder is spread on the surface of the shaped part and is leveled off. The upper section of the sintered part is selectively spliced so that it is bonded to the molded part, and the stent model is stacked layer by layer as shown in Fig. 6. Since unbound solid particles can support any cantilever structure during sintering, SLS does not require a temporary support structure, simplifying the post-treatment process.

During the processing of bone scaffolds, polycaprolactone (PCL), polylactic acid (PLA), inorganic ceramics and composite materials thereof can be used as raw materials, and the processing precision is determined by the size of the powder, the diameter of the laser beam, and the pass of the powder layer. Roskies et al. demonstrated that porous polyetheretherketone (PEEK) scaffold can be prepared using SLS technology, which is capable of maintain the biological activity of cells and is conducive to the differentiation of osteoblasts [45].

Three-dimensional powder printing

The principle of 3D printing technology is similar to that of SLS. The difference is in the selective bonding of powder by spraying adhesive instead of laser sintering. The molding principle is shown in Fig. 7. In the printing process, the powder material is first laid on the printing platform, the inkjet nozzle sprays the adhesive according to the shape of the single-layer cross section of the model, and then the heater heats and dries the adhesive, then adjusts the printing platform, relays the powder and scrapes the flat, and then bonds the upper cross section to finally form the desired solid structure. Drying is required to ensure bond strength before further processing.

Properties like powder bed thickness [46, 47], binder and powder composition [48, 49], surface roughness and flowability of powder [46], interaction of powder and binder [50] may affect the quality of the final product. Although 3DP does not require an additional support structure, it is difficult to completely remove the free powder when printing a bone support containing a microporous structure. In addition, due to the mild conditions in the printing process, extreme conditions such as laser heating are not required, which is beneficial to the addition of bioactive materials and is more suitable for the preparation of bone tissue engineering scaffolds. Hermann et al. used 3DP-prepared HA bone scaffolds with a pore size of 10–30 μm and a mechanical strength of up to 22 MPa, which can be used as a bone tissue engineering scaffold [51].

Challenges and future perspectives

Nowadays, various experimental verifications of scaffold materials and preparing methodology have been proven greatly contributing to the development of bone tissue engineering. In the meantime, still some issues need to be addressed.

Highly vascularization of bone scaffold

The effective of bone scaffold depends on the vascular system to transport nutrients, oxygen and carry away metabolic waste. Failed to establish a blood supply system will ultimately result in failure in scaffold implantation and may lead to immunological rejection. Vascularization of scaffold has become the bottleneck of clinical apply of tissue engineering. Traditional methods use biomaterial surface to conglutinate growth factors and peptides to promote the establishment of vascular system, but with little success. Fortunately in recent years, some scholars have proposed to establish a functional vascular system before implantation, that is to build a functional capillary system preferentially through 3D printing cells in vitro, and establish blood circulation through surgical techniques and receptors later [52]. Bose et al. [53] treated 3D-printed tricalcium phosphate bone scaffold with hydrochloric acid buffer containing Mg^{2+} and Sr^{4+} ions for

4–12 weeks, and 14–20% of the scaffold material surface has obvious vascular establishment. However, how to achieve the mutual signal transduction between cells, the invasion of vessels and how to make sure cells and bioactive factors keep active during the printing process to realize the final functionalization of the printed organs still remains a challenge.

Applicable powder material property and binder formula

When 3DP printing technology is applied to the manufacture of bone scaffolds, the material and structure determine the biological and mechanical properties of the bone scaffold, which directly affects the role of bone scaffold in the repair of bone defects. Firstly, the fluidity of the powder enables high-resolution printing, which mainly depends on the particle size and shape. The smaller the particle size, and the closer the shape is to the sphere, the better the fluidity. However, too small of the powder size tends to agglomerate due to internal special forces, resulting in reduced fluidity [54]. Secondly, binders must not only be able to effectively bond the substrate to meet the mechanical properties, porosity, and pore connectivity requirement, but also need to be non-cytotoxic, good biocompatibility, reasonable degradation rate, etc. Finally, the ratio of the binder needs to be adjusted, considering that the reactivity of the powder and the binder, the viscosity, density, surface tension and other parameters of the binder will affect the quality of the bond process.

Precision and quality control of three-dimensional forming of scaffold

Errors may occur due to various reasons during the preparation of the scaffold using different rapid prototyping methods. In the process of stereolithography, linear shrinkage and volume shrinkage occur during the polymerization of the resin from liquid to solid. Linear shrinkage will result in interlaminar stresses when layer-by-layer stacking causes the molded part to warp and deform, and volume shrinkage will cause changes in the size of the formed part, resulting in low precision. Three-dimensional powder printing experiences the stages of binder spray, impacting on powder bed, expansion, fusion and curing. Each stage may affect the forming quality [6], such as the satellite droplets generated during the injection, the compressive load generated when impacting the powder bed that will cause the longitudinal displacement of the printed thin layer, the excessive diffusion of the binder on the powder bed and the strength of the bond. To obtain scaffold with the desired accuracy and strength, it is necessary to study the influencing factors and find specific solution for each molding method.

Acknowledgements The authors acknowledge the financial support provided by the 111 Project (Grant No. B13044) and the National key research and development project (2017YFB1104205) to conduct this research.

Author contributions YW and KJ conceived and designed the paper; KJ, QW, KZ, AJ, YR, XC collected the studies; KJ and YW wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

References

1. Tang D, Tare RS, Yang LY et al (2016) Biofabrication of bone tissue: approaches, challenges and translation for bone regeneration. Biomaterials 83:363–382
2. Ku KC, Lee MW, Kuo SM et al (2013) Preparation and evaluation of collagen I/gellan gum/beta-TCP microspheres. Conf Proc IEEE Eng Med Biol Soc. 2013:6667–6770
3. Temple JP, Hutton DL, Hung BP et al (2014) Engineering anatomically Shaped vascularized bone grafts with hASCs and 3D-printed PCL scaffolds. J Biomed Mater Res A 102(12):4317–4325
4. Tamaddon Maryam, Wang Ling, Liu Ziyu, Liu Chaozong et al (2018) Osteochondral tissue repair in osteoarthritic joints: clinical challenges and opportunities in tissue engineering. Bio-Des Manuf 1:101–114
5. Mitra J, Tripathi G, Sharma A et al (2013) Scaffolds for bone tissue engineering: role of surface patterning on osteoblast response. Rsc Adv 3(28):11073–11094
6. Kumar A, Mandal S, Barui S et al (2016) Low temperature additive manufacturing of three dimensional scaffolds for bone-tissue engineering applications: processing related challenges and property assessment. Mater Sci Eng R 103:1–39
7. Fernandes AM, Fernandes TG, Diogo MM et al (2007) Mouse embryonic stem cell expansion in a microcarrier-based stirred culture system. J Biotechnol 132(2):227–236
8. Huss FR, Junker JP, Johnson H et al (2007) Macroporous gelatine spheres as culture substrate, transplantation vehicle, and biodegradable scaffold for guided regeneration of soft tissues. In vivo study in nude mice. J Plast Reconstr Aesthet Surg J 60(5):543–555
9. Diogo GS, Gaspar VM, Serra IR, Fradique R, Correia IJ (2014) Manufacture of β-TCP/alginate scaffolds through a Fab@home model for application in bone tissue engineering. Biofabrication 6(2):025001
10. Chandorkar Y, Bhaskar N, Madras G, Basu B (2015) Long-term sustained release of salicylic acid from cross-linked biodegradable polyester induces a reduced foreign body response in mice. Biomacromolecules 16(2):636–649
11. Burg KJL, Porter S, Kellam JF (2000) Biomaterial developments for bone tissue engineering [J]. Biomaterials 21(23):2347–2359
12. Subramanian G, Bialorucki C, Yildirim-Ayan E (2015) Nanofibrous yet injectable polycaprolactone-collagen bone tissue scaffold with osteoprogenitor cells and controlled release of bone morphogenetic protein-2. Mater Sci Eng C 51:16–27
13. Giannitelli SM, Basoli F, Mozetic P et al (2015) Graded porous polyurethane foam: a potential scaffold for oro-maxillary bone regeneration. Mater Sci Eng C Mater Biol Appl 51:329–335
14. Veronesi F, Giavaresi G, Guarino V et al (2015) Bioactivity and bone healing properties of biomimetic porous composite scaffold: in vitro and in vivo studies. J Biomed Mater Res Part A 103(9):2932

15. Hutmacher DW (2000) Scaffolds in tissue engineering bone and cartilage. Biomaterials 21(24):2529–2543
16. Kumar A, Biswas K, Basu B (2013) On the toughness enhancement in hydroxyapatite-based composites. Acta Mater 61(14):5198–5215
17. Dubey AK, Anumol EA, Balani K et al (2013) Multifunctional properties of multistage spark plasma sintered HA–$BaTiO_3$-Based piezobiocomposites for bone replacement applications. J Am Ceram Soc 96(12):3753–3759
18. Chandorkar Y, Madras G, Basu B (2013) Structure, tensile properties and cytotoxicity assessment of sebacic acid based biodegradable polyesters with ricinoleic acid. J Mater Chem B 1(6):865–875
19. Boskey AL (2006) Mineralization, structure and function of bone. Dyn Bone Cartil Metab 2:201–212
20. Wang YE, Xinpei LI, Yang MM et al (2015) Three dimensional fabrication custom-made bionic bone preoperative diagnosis models for orthopaedics surgeries. Sci Sin Inf 45(2):235
21. Qin M, Liu Y, He J et al (2014) Application of digital design and three-dimensional printing technique on individualized medical treatment][J. Chinese Journal of Reparative & Reconstructive Surgery 28(3):286
22. Blaker JJ, Maquet V, Jérôme R et al (2005) Mechanical properties of highly porous PDLLA/Bioglass composite foams as scaffolds for bone tissue engineering [J]. Acta Biomater 1(6):643–652
23. Liu Q, de Wijn JR, De GK et al (1998) Surface modification of nano-apatite by grafting organic polymer. Biomaterials 19(11–12):1067
24. Mitra J, Tripathi G, Sharma A, Basu B (2013) Scaffolds for bone tissue engineering: role of surface patterning on osteoblast response. RSC Adv 3:11073–11094
25. Datta N, Pham QP, Sharma U et al (2006) In vitro generated extracellular matrix and fluid shear stress synergistically enhance 3D osteoblastic differentiation. Proc Natl Acad Sci USA 103(8):2488–2493
26. Zhang N, Nichols HL, Tylor S et al (2007) Fabrication of nanocrystalline hydroxyapatite doped degradable composite hollow fiber for guided and biomimetic bone tissue engineering. Mater Sci Eng, C 27(3):599–606
27. Ravaglioli A, Krajewski A (1997) Implantable porous bioceramics. Mater Sci Forum 250:221–230
28. Holmes R (1979) Bone regeneration within a coralline hydroxyapatite implant. Plast Reconstr Surg 63:626–633
29. Akeda K, An HS, Okuma M et al (2006) Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthr Cartil 14(12):1272–1280
30. Chang BS, Hong KS et al (2000) Osteoconduction at porous hydroxyapatite with various pore configurations [J]. Biomaterials 21(12):1291
31. Jian YK, Tian XB, Li B et al (2008) Properties of deproteinized bone for reparation of big segmental defect in long bone. Chin J Traumatol 11(3):152–156
32. Wang YE, Li XP, Yang MM et al (2015) Three dimensional fabrication custom-made bionic bone preoperative diagnosis models for orthopaedics surgeries. Sci China 45:35–247
33. Guarino V, Ambrosio L (2010) Temperature-driven processing techniques for manufacturing fully interconnected porous scaffolds in bone tissue engineering. Proc Inst Mech Eng H 224(12):1389–1400
34. Jang JH, Castano O, Kim HW (2009) Electrospun materials as potential platforms for bone tissue engineering. Adv Drug Deliv Rev 61(12):1065–1083
35. Sachlos E, Czernuszka J (2003) Making tissue engineering scaffolds work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds. Eur Cells Mater 5:29–39
36. Garrett B (2014) 3D printing: new economic paradigms and strategic shifts. Global Policy 5:70–75
37. Klammert U, Gbureck U, Vorndran E, Rodiger J, Meyer-Marcotty P, Kubler AC (2010) 3D powder printed calcium phosphate implants for reconstruction of cranial and maxillofacial defects. J Cranio-Maxillofacial Surg 38:565–570
38. Wang J, Yang M, Zhu Y, Wang L, Tomsia AP, Mao C (2014) Phage nanofibers induce vascularized osteogenesis in 3D printed bone scaffolds. Adv Mater 26:4961–4966
39. Shim JH, Kim SE, Park JY, Kundu J, Kim SW, Kang SS, Cho D-W (2014) Three-dimensional printing of rhBMP-2-loaded scaffolds with long-term delivery for enhanced bone regeneration in a rabbit diaphyseal defect. Tissue Eng A 20:1980–1992
40. Li Y, Wu ZG, Li XK et al (2014) A polycaprolactone-tricalcium phosphate composite scaffold as an autograft-free spinal fusion cage in a sheep model. Biomaterials 35(22):5647
41. Zein I, Hutmacher DW, Tan KC et al (2002) Fused deposition modeling of novel scaffold architectures for tissue engineering applications. Biomaterials 23(4):1169–1185
42. Dong Yifan, Duan Haibo, Zhao Naru et al (2018) Three-dimensional printing of β-tricalcium phosphate/calcium silicate composite scaffolds for bone tissue engineering. Bio-Design Manuf 1:146–156
43. Jin WL, Kang KS, Lee SH et al (2011) Bone regeneration using a microstereolitho graphy-produced customized poly(propylene fumarate)/diethyl fumarate photopolymer 3D scaffold incorporating BMP-2 loaded PLGA microspheres. Biomaterials 32(3):744–752
44. Ronca A, Ambrosio L, Grijpma DW (2012) Design of porous three-dimensional PDLLA/nano-hap composite scaffolds using stereolithography. J Appl Biomater Funct Mater 10(3):249–258
45. Roskies M, Jordan JO, Fang D et al (2016) Improving PEEK bioactivity for craniofacial reconstruction using a 3D printed scaffold embedded with mesenchymal stem cells. J Biomater Appl 31(1):38–39
46. Lanzetta M, Sachs E (2003) Improved surface finish in 3D printing using bimodal powder distribution. Rapid Prototyp J 9:157–166
47. Butscher A, Bohner M, Hofmann S, Gauckler L, Müller R (2011) Structural and material approaches to bone tissue engineering in powder-based three-dimensional printing. Acta Biomater 7:907–920
48. Lam CXF, Mo X, Teoh S-H, Hutmacher D (2002) Scaffold development using 3D printing with a starch-based polymer. Mater Sci Eng, C 20:49–56
49. Khalyfa A, Vogt S, Weisser J, Grimm G, Rechtenbach A, Meyer W, Schnabelrauch M (2007) Development of a new calcium phosphate powder-binder system for the 3D printing of patient specific implants. J Mater Sci Mater Med 18:909–916
50. Landers R, Mühaupt R (2000) Desktop manufacturing of complex objects, prototypes and biomedical scaffolds by means of computer-assisted design combined with computer-guided 3D plotting of polymers and reactive oligomers. Macromol Mater Eng 282:17–21
51. Seitz H, Rieder W, Irsen S et al (2005) Three-dimensional printing of porous ceramic scaffolds for bone tissue engineering. J Biomed Mater Res B Appl Biomater 74B(2):782–788
52. Barabaschi GD, Manoharan V, Li Q et al (2015) Engineering prevascularized scaffolds for bone regeneration. Adv Exp Med Biol 881:79–94
53. Bose S, Tarafder S, Bandyopadhyay A (2017) Effect of chemistry on osteogenesis and angiogenesis towards bone tissue engineering using 3D printed scaffolds. Ann Biomed Eng 45(1):261–272
54. Butscher A, Bohner M, Hofmann S et al (2011) Structural and material approaches to bone tissue engineering in powder-based three-dimensional printing. Acta Biomater 7(3):907–920